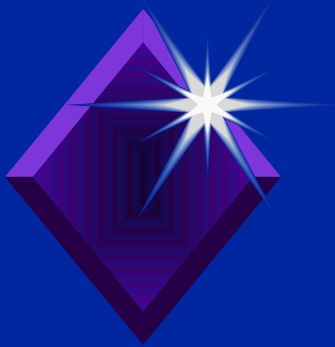


VENOUS THROMBOEMBOLIS M

**Thomas M. Howard, MD
VCU-Fairfax Family Practice**



Objectives

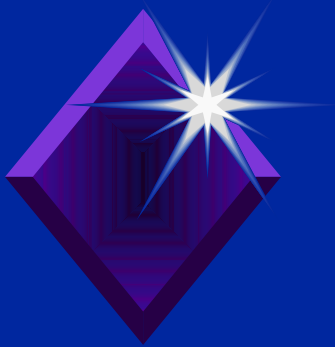
- 1. To understand the role of diagnostic testing in the evaluation of Venous Thromboembolism**
- 2. To understand the management options for Venous Thromboembolism**
- 3. To understand the risk factors for Venous Thromboembolism to establish prevention strategies.**



Goals of Management

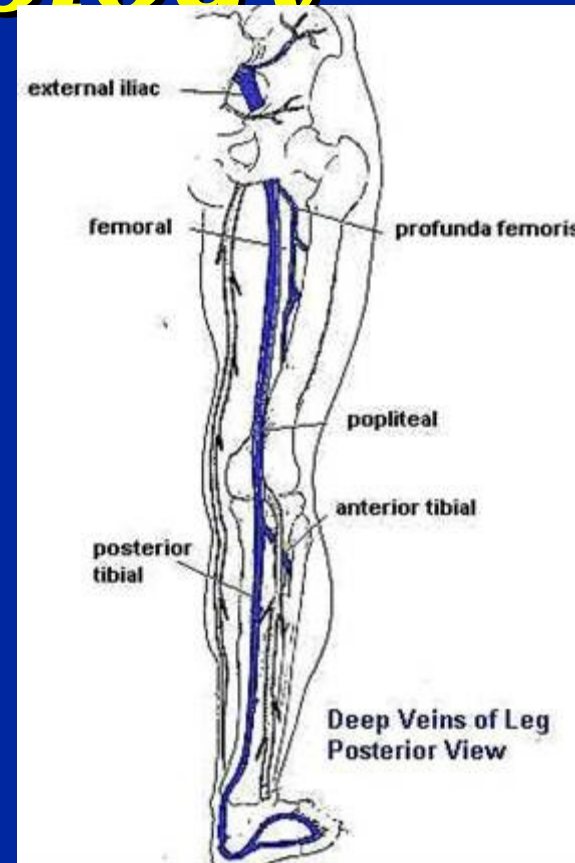
- ◆ **Prevent mortality/morbidity from PE**
- ◆ **Prevent sequelae of venous insufficiency (post thrombotic syndrome)**

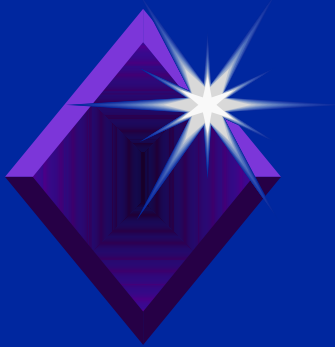




Deep Vein Thrombosis Epidemiology

- ◆ Over 600,000 hospitalizations per year
- ◆ Up to 50-70% proximal DVT's will result in PE (most asymptomatic)
- ◆ Common primary care diagnosis

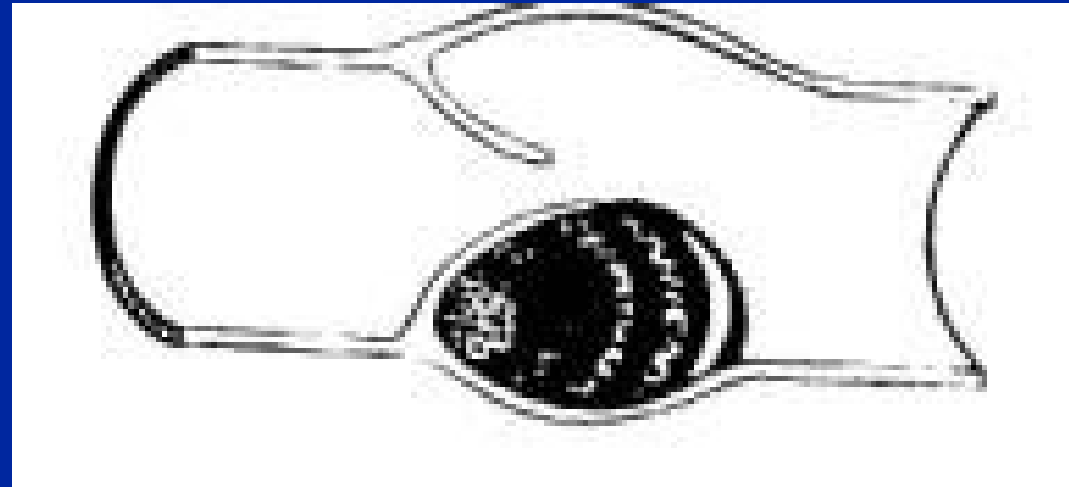




Risk Factors

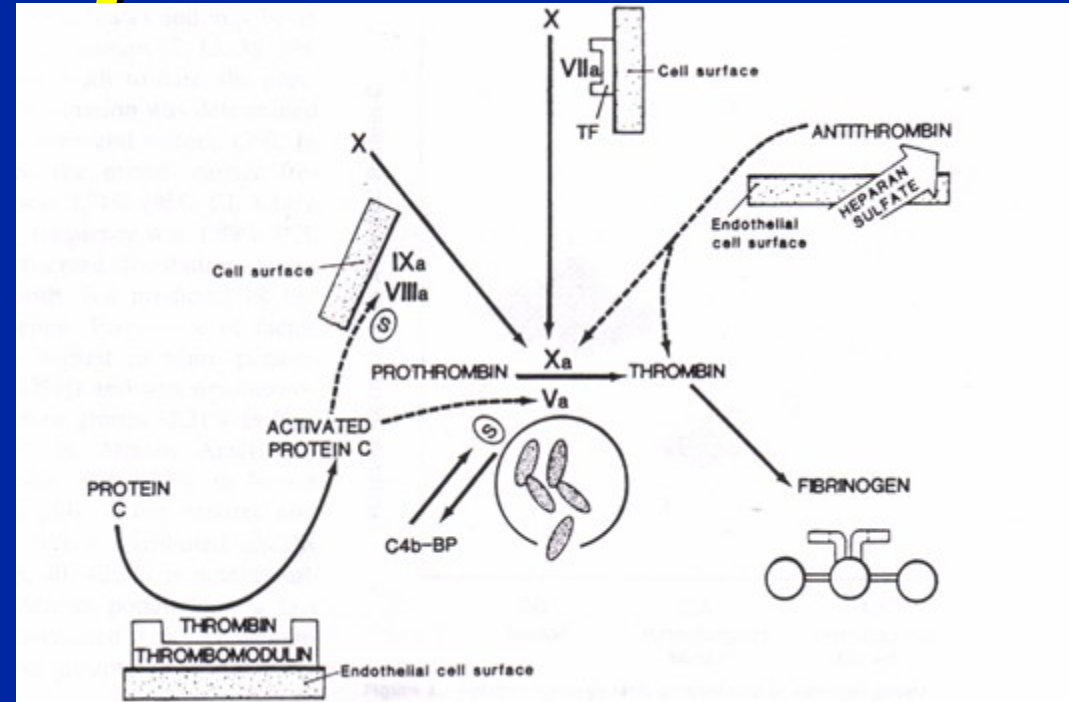
◆ **Virchow's Triad**

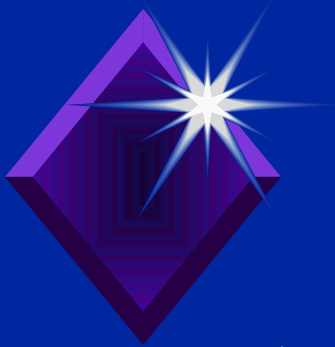
- ◆ **Hypercoagulability -**
OCP's, HRT,
Hypercoagulable
state
- ◆ **Stasis - Immobility,**
CHF, Obesity,
Pregnancy, Air
travel >4 hrs
- ◆ **Endothelial damage**
- Limb trauma,
major surgery



Hypercoagulable State Thrombophilia

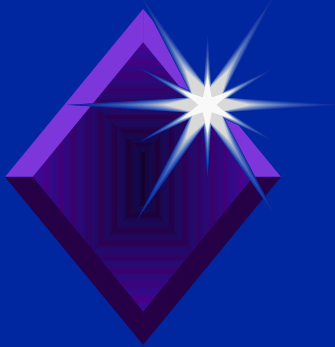
- ◆ Cancer -Pancreatic, Colonic, Urologic (mucin secreting)
- ◆ Deficiency of Protein C, Protein S, Antithrombin III, Prothrombin 20210A Mutation
- ◆ Hyperhomocysteinemia
- ◆ Anticardiolipin Antibody Syndrome
- ◆ Nephrotic Syndrome
- ◆ Myeloproliferative Disorders





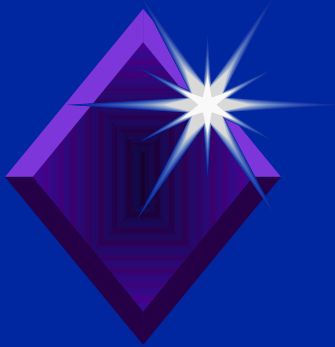
Factor V Leiden

- ◆ **G1691A mutation**
 - ◆ glutamine for arginine on Factor V
- ◆ **Resistance to activated Protein C degradation**
- ◆ **Overall 3.71% prevalence**
- ◆ **Heterozygous Fe on OCP 35-50X increased risk of VTE**
- ◆ **Homozygous Fe on OCP several hundred fold increased risk of VTE**



Prothrombin 20210A Mutation

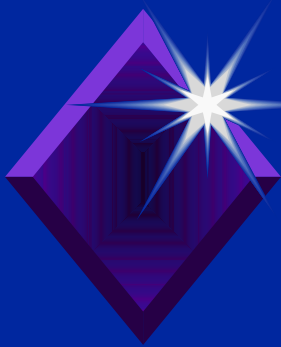
- ◆ **30% increased Prothrombin levels**
- ◆ **.7-6% prevalence**
- ◆ **Increased RR ~2.8**
- ◆ **Uncommon in non-white population**



Symptoms

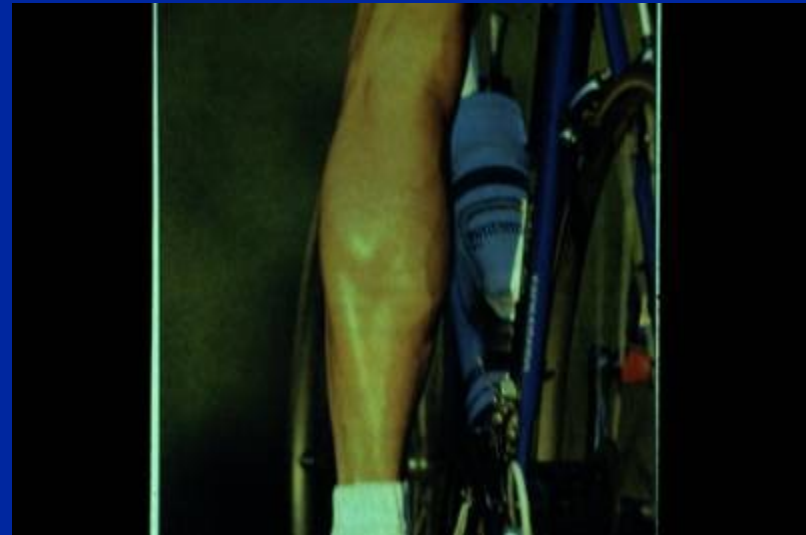
- ◆ **Leg pain with swelling in a high risk patient (usually unilateral)**





Differential Diagnosis

- ◆ **Knee**
 - ◆ Baker's Cyst
 - ◆ DJD or injury
- ◆ **Muscle Injury/Tear (Gastrocnemius)**
- ◆ **Cellulitis**
- ◆ **Edema in a paralyzed extremity**
- ◆ **Lymphedema/Lymphangitis**
- ◆ **Venous Insufficiency**



Pretest Probability

Active cancer

Paralysis or casting

Recent immobilization or surgery

Tenderness along the deep veins

Swelling of the entire leg

Calf circumference diff > 3 cm

Pitting edema

No alternative dx

Distension of venous

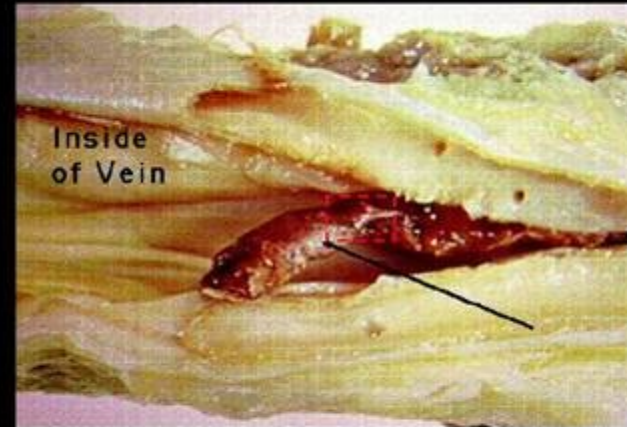
al

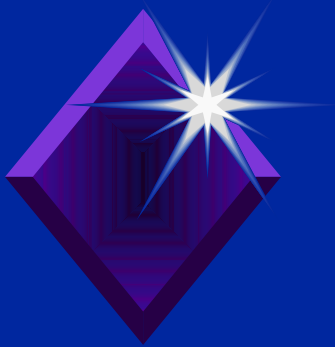
0 low risk

1-2 mod risk

>2 high risk

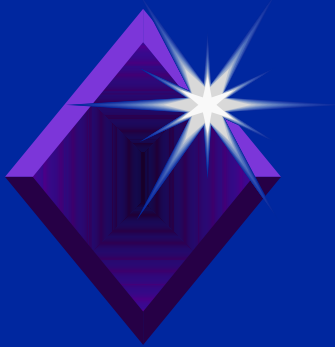
Deep Leg vein Thrombosis





D-dimer

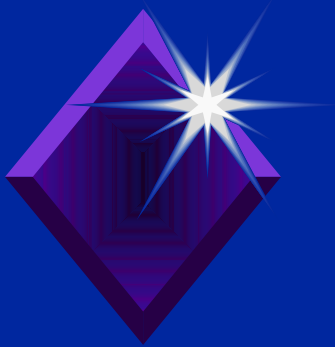
- ◆ **Fibrin degradation product (FSP)**
- ◆ **Increased in DVT, PE, MI, sepsis, postpartum, metastatic cancer, CVD**
- ◆ **Not reliable if h/o Ca, age >70, or on Coumadin**
- ◆ **Level < 500ug/l considered negative**
- ◆ **NPV alone near 96%**
- ◆ **NPV near 100% if neg with low clinical suspicion**



Duplex Ultrasound

- ◆ Ann Int Med 1998 128(1):1
 - ◆ 405 pts with first DVT
 - ◆ US day 0 and 5-7
 - ◆ 3 month f/u
 - ◆ 342 with initial nl and 7 abn at f/u
 - ◆ 0 deaths for PE and 2 VTE @ 3months
 - ◆ I (0.6%)
- repeat in 3-7 days**





DVT
Suspected

D-
Dimer

Negati
ve

Positiv
e

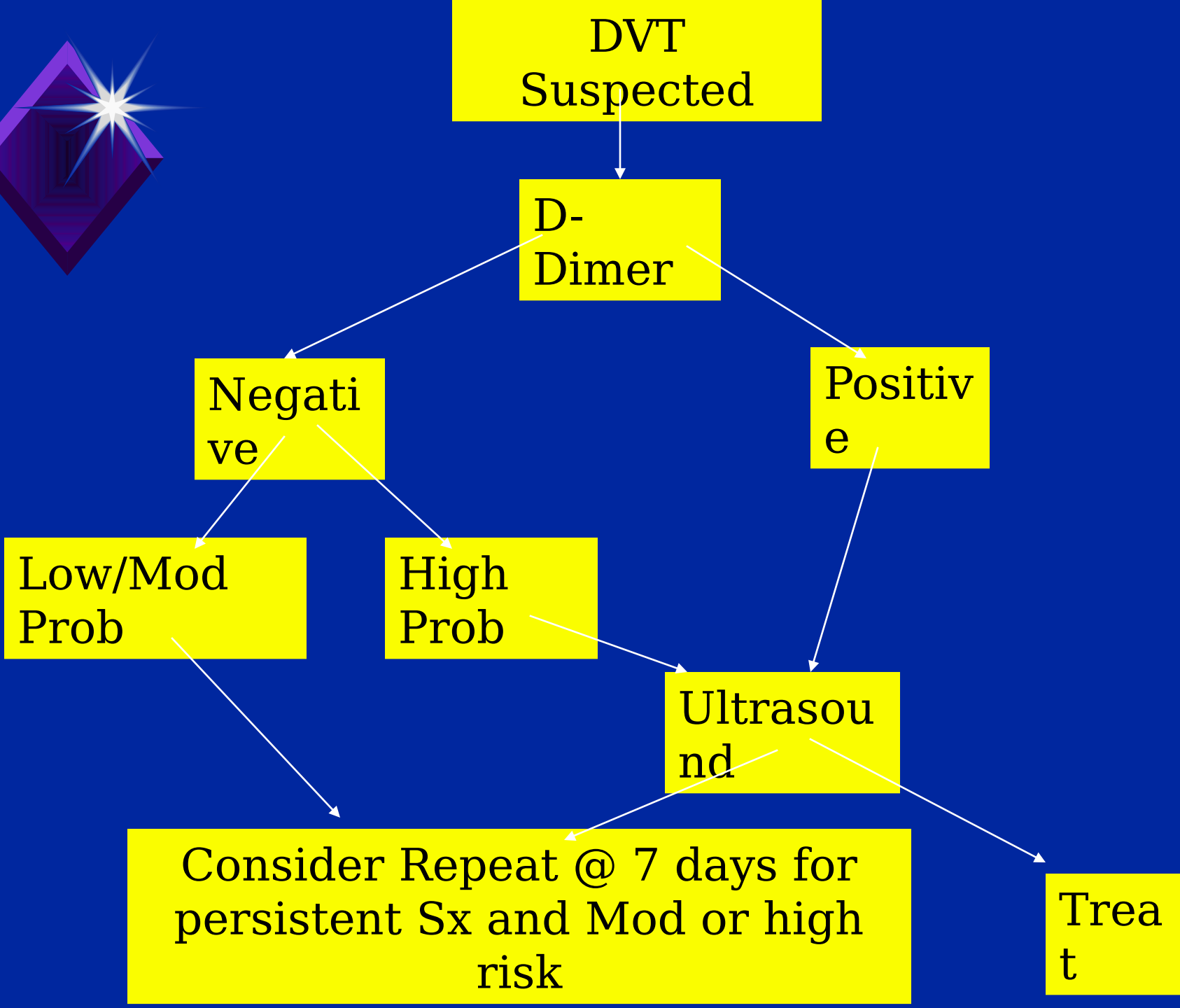
Low/Mod
Prob

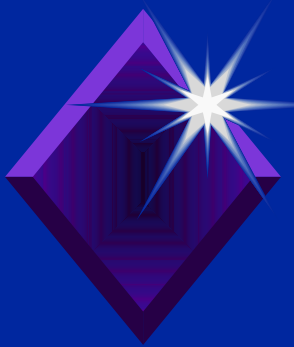
High
Prob

Ultrasou
nd

Consider Repeat @ 7 days for
persistent Sx and Mod or high
risk

Trea
t

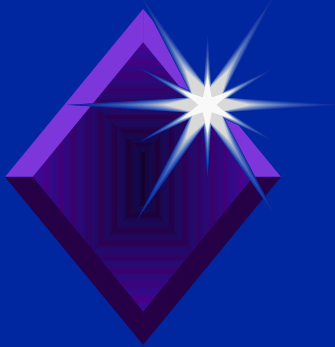




Magnetic Resonance Venography (MRV)

- ◆ No contrast material used (Gadolinium enhanced)
- ◆ More effective for pelvic vessels, head, neck
- ◆ Can differentiate old from new thrombus
- ◆ Can do legs or legs and lung simultaneously
- ◆ Sensitivity = 97%
- ◆ Specificity = 95%





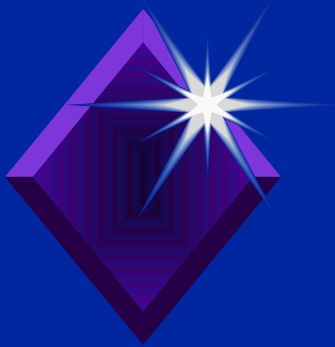
Traditional Treatment

- ◆ H **Arch Int Med 1997;157:305**
 - 95 pts (62 FFT and 28 occlusive thrombus)
- ◆ R Rx LMWH or Heparin
 - d US, venogram, VQ then PAgram
 - a PE
 - ◆ 64% with FFT
 - ◆ 50% occlusive
- Recurrent PE
 - ◆ 3.3% FFT
 - ◆ 3.7% occlusive



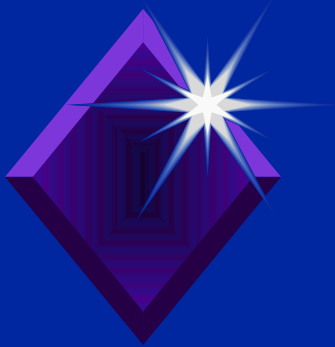
Heparin Side Effects

- ◆ Hemorrhage 6%
- ◆ Heparin Associated Thrombocytopenia (HAT)
 - ◆ Platelet count $<100,000$ or $>50\%$ decrease over baseline after day 5
 - ◆ Platelet activation (PF 4)
 - ◆ Hypercoagulable state 7-10 days into treatment
 - ◆ Venous and arterial thrombi
 - ◆ Platelet activation factor (PAF)



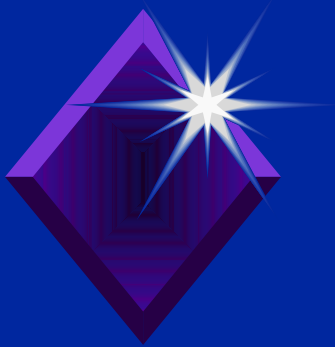
Problems

- ◆ **Does not preserve valves/valve function, therefore does not prevent chronic venous insufficiency**
- ◆ **Heparin side effects**
- ◆ **Risk of recurrent DVT**
 - ◆ **approx. 36%**



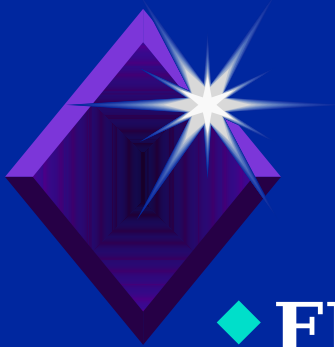
Coumadin

- ◆ **Coumadin starting day 1**
- ◆ **4 day overlap with Heparin**
- ◆ **Duration of Coumadin therapy?**
 - ◆ **1st episode 3 months**
 - ◆ **2nd episode 1 year**
 - ◆ **3rd episode indefinite**
- ◆ **To maintain INR 2-3**
- ◆ **Avg cost \$0.55/day**



Coumadin Side Effects

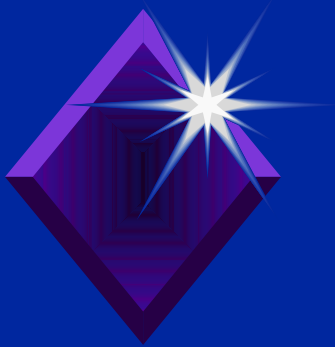
- ◆ **INR adjustments based on diet, medications,...**
- ◆ **Early pro-coagulant effect - overlap 3-4 days with Heparin**
 - ◆ **Transient Protein C & S deficiency**
- ◆ **Hemorrhage 6-29%**
- ◆ **Purple Toes Syndrome**
- ◆ **Skin necrosis (usually early due to transient Protein C deficiency)**
- ◆ **Teratogenic**



Coumadin

Reversal

- ◆ FFP - rapid, but with blood product risk
- ◆ Vit K
 - ◆ Large dose (5-10 mg IV) makes re-anticoagulation difficult
 - ◆ Low dose (0.5-1 mg IV) will reduce INR in hrs
- ◆ Heparin window for high risk patients undergoing elective procedures



Low-Molecular-Weight Heparins

LMWH

◆ Enzymatically fragmented heparins

◆ Dosing OD or BID. fixed dose or

w **Enoxaparin (Lovenox)**

◆ L **Dalteparin (Fragmin)**

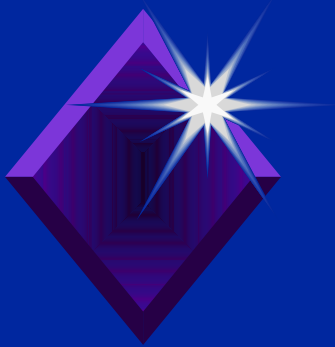
(> **Fraxiparine**
(Nadroparin)

◆ **Logiparin**
(Tinzaparin)

Ardeparin (Normiflo)

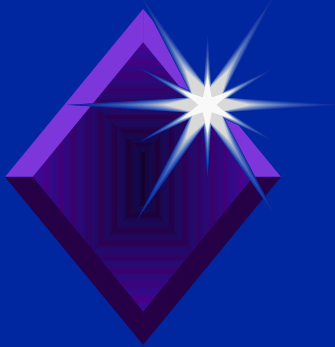
Clivarine (Reviparin)

alyzing one



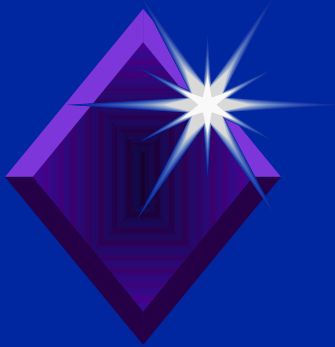
LMWH

- ◆ **No need to monitor PTT (decreased Thrombin binding)**
 - ◆ Binds to antithrombin III as a catalyst for anti-factor Xa
- ◆ **Should monitor anti Xa levels**
 - ◆ Range .5-1.2
- ◆ **Side Effects**
 - ◆ Hemorrhage-4%
 - ◆ local irritation at injection site
 - ◆ elevated transaminases-5%
 - ◆ rare osteopenia or thrombocytopenia
- ◆ **Contraindicated if h/o HAT**



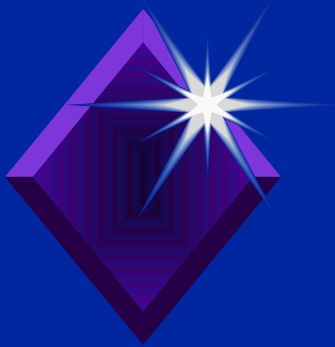
Hirudin/rHirudin

- ◆ From saliva of leeches
- ◆ Direct thrombin inhibitor
- ◆ Lepirudin (Refludan)
 - ◆ 0.4 mg/kg bolus with infusion or 0.15 mg/Kg/hr for 2-10 days
- ◆ Use if h/o HAT
- ◆ Improved RR and overall rate of DVT s/p THR vs LMWH
 - NEJM
 - 1997;337(19):1329



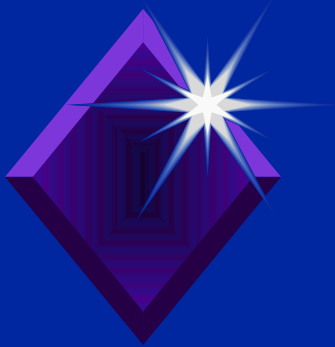
Danaparoid

- ◆ **Depolymerized mixture of heparin, dermatan sulfate, and chondroitin sulfate**
- ◆ **Inhibitor of Factor Xa**
- ◆ **750 anti-Xa U BID**
- ◆ **\$216/day**
- ◆ **No PF-4 activity**



Thrombolytics

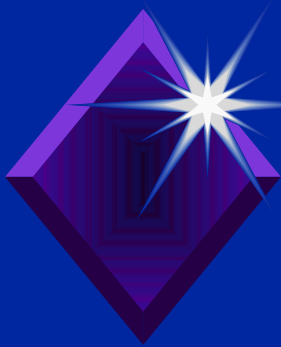
- ◆ **Systemic or catheter directed**
- ◆ **Benefits**
 - ◆ **Preservation of valves (prevent post thrombotic syndrome)**
 - ◆ **Decreased incidence of recurrent DVT (approx. 7%)**
- ◆ **Symptoms < 10 days**



Prevention

- ◆ **Ident** Compression Stockings for long air
high travel
- ◆ **Early** 10% prevalence of asx DVT
- ◆ **Comp**
stock 0 with use of stockings
 - ◆ Pne
 - ◆ Gra
- ◆ **CPM** Lancet 357:1485-9
- ◆ **Heparin, LMWH,**
or others

Stockings
g a gradient

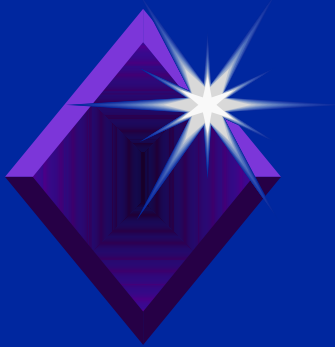


Pulmonary Embolism

Epidemiology

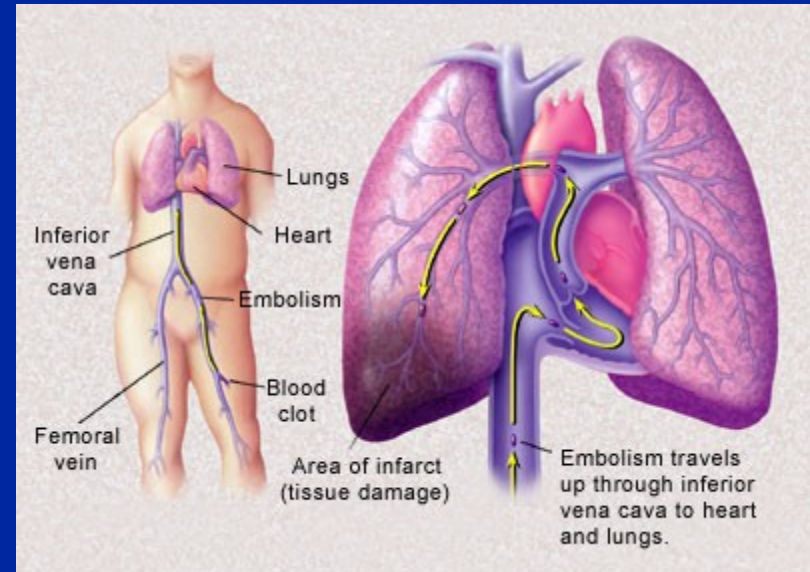
- ◆ 300,000 hospitalizations and 100,000-200,000 deaths/year
- ◆ Case fatality of 15% (not changed in last decade)
- ◆ Majority of emboli from deep veins of the lower extremity
- ◆ Majority of deaths in undiagnosed





Epidemiology

- ◆ **PE risk with proximal LE DVT = 50%**
- ◆ **Upper extremity venous thrombosis**
 - ◆ **PE risk = 12-17%**
- ◆ **70% PE deaths not diagnosed prior to death**



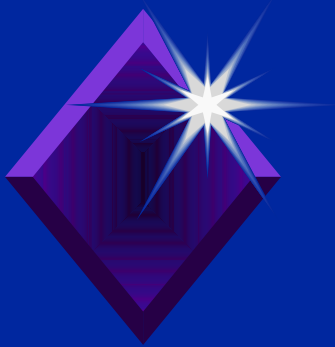


Symptoms

- ◆ **Dyspnea**
81%
- ◆ **Chest Pain** 72%
- ◆ **Apprehension**
59%
- ◆ **Cough** 54%
- ◆ **Hemoptysis** 34%
- ◆ **Diaphoresis** 26%

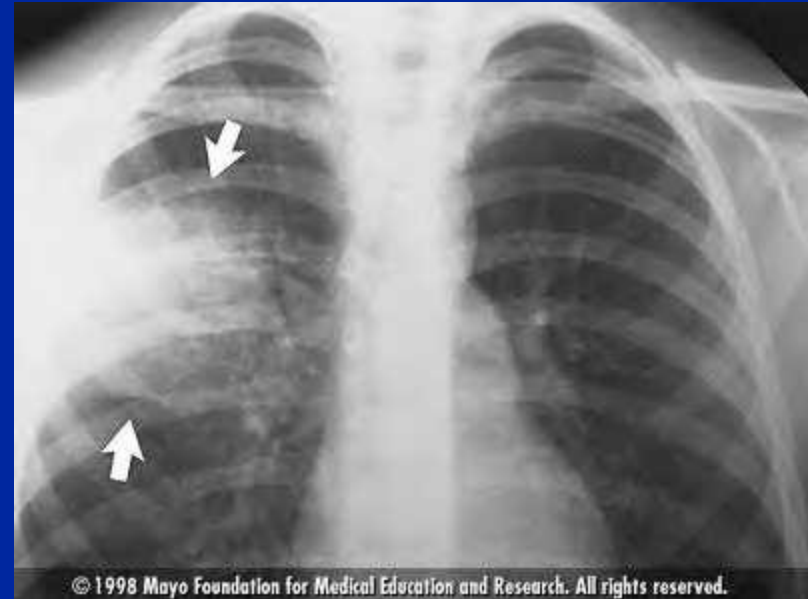
Physical Findings

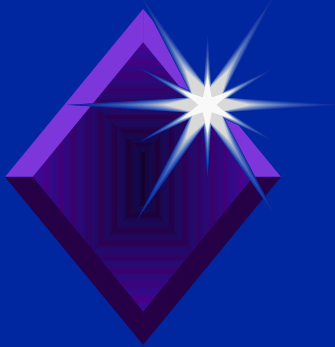
- ◆ **Tachypnea** 87%
- ◆ **Rales** 53%
- ◆ **Loud P2**
53%
- ◆ **Tachycardia** 44%
- ◆ **Fever** 42%



Differential Diagnosis Pulmonary

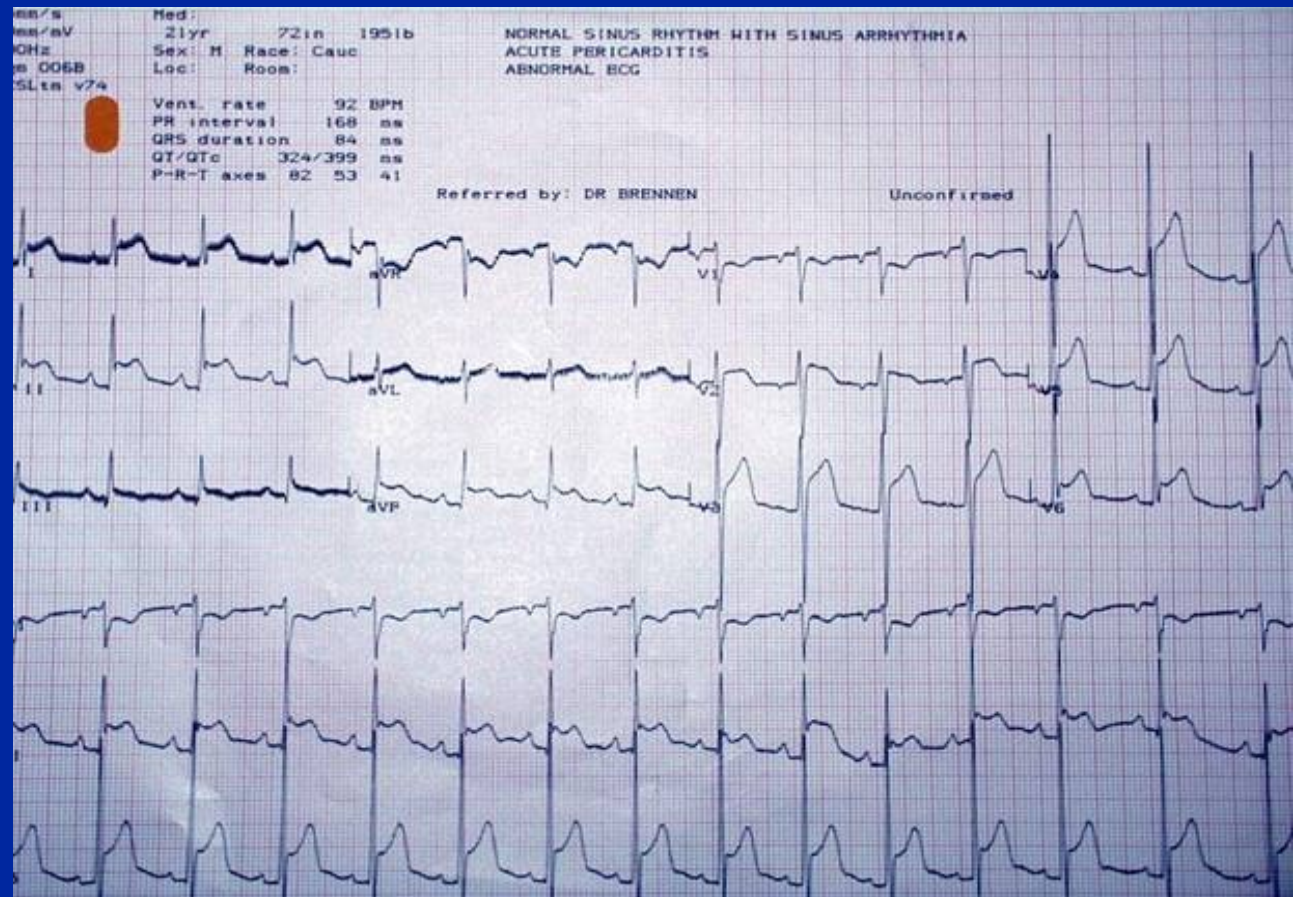
- ◆ **Pneumonia**
- ◆ **COPD/Asthma**
- ◆ **Pneumothorax**
- ◆ **Pleurisy**
- ◆ **Tb**
- ◆ **Cancer**

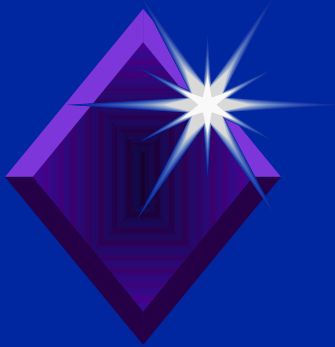




Differential Diagnosis Cardiac

- ◆ Myocardial Infarction
- ◆ Pericarditis
- ◆ CHF
- ◆ Tamponade

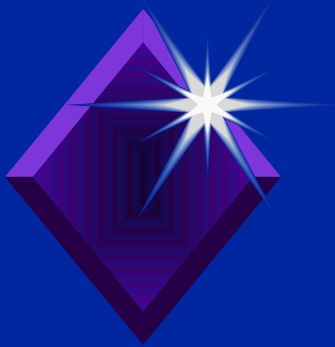




Differential Diagnosis Musculoskeletal

- ◆ Costochondritis
- ◆ Rib Fracture
- ◆ Myositis
- ◆ Trigger Point Pain

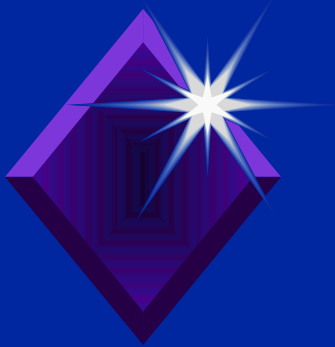




Differential Diagnosis Other

- ◆ Herpes Zoster
- ◆ Sepsis
- ◆ Radiation of abdominal pain





Wells PE Criteria

***437/930 pts with neg D-dimer and low pres-
test prob***

1 PE in f/u

NPV=99.5%

Ann Int Med 2001;135:98

<2

2-6

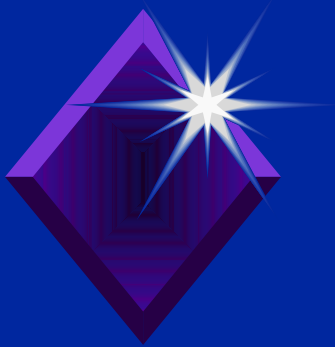
>6

Hemoptysis

1.0

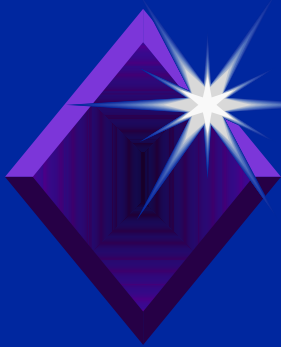
H/o cancer

1.0



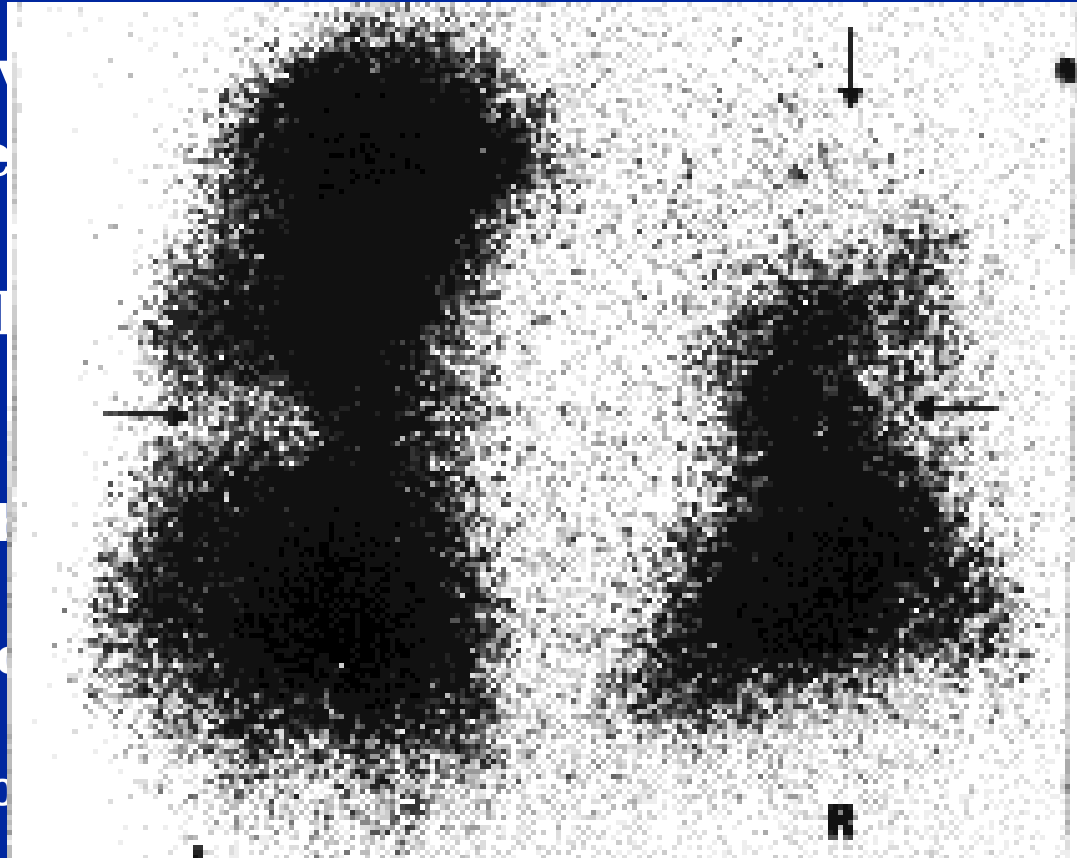
Evaluation

- ◆ **CXR, labs, EKG, Thorocentesis
not really helpful**

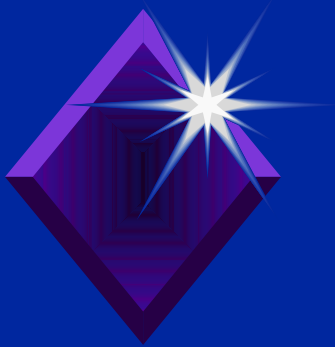


Ventilation Perfusion Scan (VQ Scan)

- ◆ Look for V (ventilate) and P (perfused)
- ◆ Risk of PE
 - ◆ Normal 0%
 - ◆ Low prob <10%
 - ◆ Intermediate 20-30%
 - ◆ High prob 90%

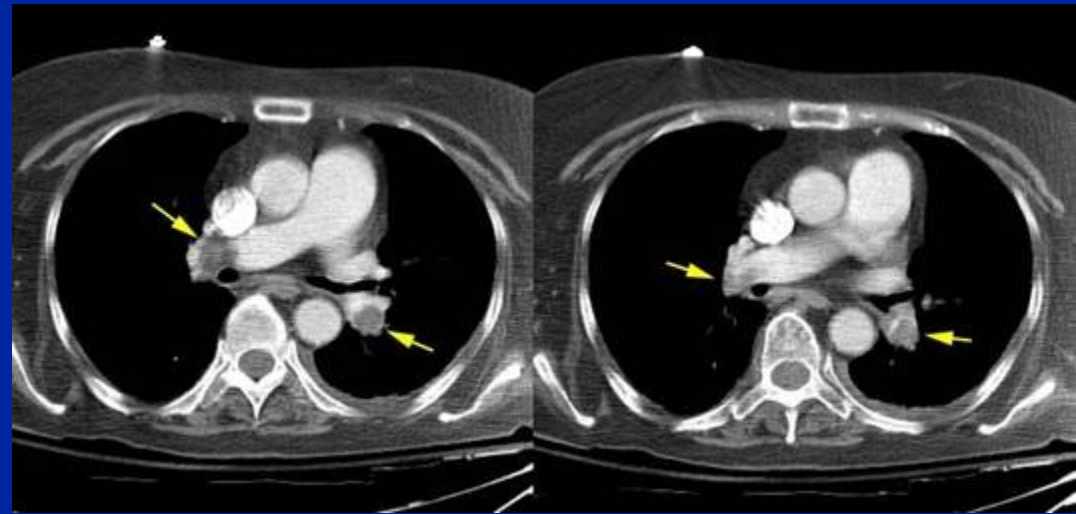


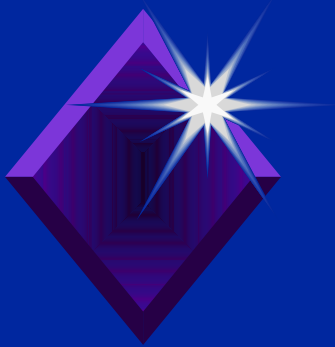
PE's
non-
c VQ
al LE
n



Spiral CT

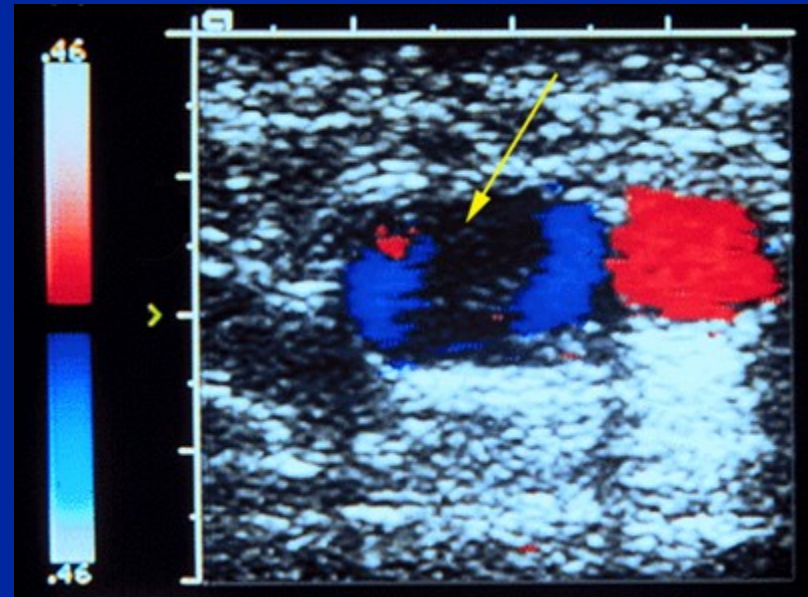
- ◆ Radiology 1996;
201:467-70
- ◆ VQ vs. spiral CT in
149 patients
- ◆ PAgram done if VQ
indeterminate
- ◆ Effective in detecting
up to segmental level
PE
- ◆ Sensitivity 82% & 94%
- ◆ Specificity 93% & 96%

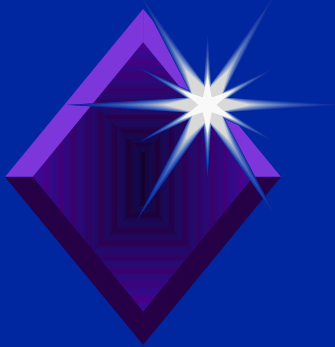




Venography or non-invasive study of the lower extremity

- ◆ Same positive findings as for DVT
- ◆ Positive LE DVT in a suspicious patient is usually adequate for diagnosis

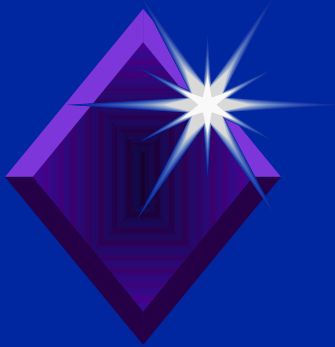




Pulmonary Angiography

- ◆ Gold standard
- ◆ Death rate 2-5/1000
- ◆ Not widely available
- ◆ Consider use if:
 - ◆ low prob VQ in suspicious patient
 - ◆ consideration for use of thrombolytics
 - ◆ contraindication to anticoagulants



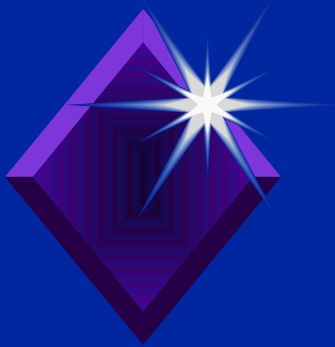


MR Angiography

- ◆ **PAgram vs. MRA with Gadolinium**
- ◆ **Three sets of readings**
- ◆ **Sensitivities 100, 87, & 75%**
- ◆ **Specificities 95, 100, & 95%**
- ◆ **Segmental or**

**NEJM 1997, May
15:1422-27**





Pulmonary Embolism Encounter Form

Patient's name: _____ Age: _____ Medical record #: _____

Data collection:

Symptom	Points
<input type="checkbox"/> Clinical signs and symptoms of deep venous thrombosis (DVT: leg swelling and pain with palpation of the deep veins)	3.0
<input type="checkbox"/> Pulmonary embolism (PE) as likely or more likely than an alternative diagnosis (based on the history and physical examination, chest radiography, electrocardiography, and any blood tests that were considered necessary)	3.0
<input type="checkbox"/> Heart rate > 100 beats per minute	1.5
<input type="checkbox"/> Immobilization (bed rest, except to access the bathroom, for at least 3 consecutive days) or surgery in the previous 4 weeks	1.5
<input type="checkbox"/> Previous objectively diagnosed DVT or PE	1.5
<input type="checkbox"/> Hemoptysis	1.0
<input type="checkbox"/> Malignancy (treatment that is ongoing, within the past 6 months, or palliative)	1.0
Total points:	
Risk score interpretation:	
<2 points: low risk (1.3 percent)	
2 to 6 points: moderate risk (16.2 percent)	
>6 points: high risk (40.6 percent)	

Other important data:

- ☐ Known thrombophilia
☐ Pregnant

Other information from the history and physical examination:

Low-risk patient:

Order D-dimer assay (at least 85% sensitive):

- ☐ D-dimer negative: PE ruled out. *
☐ D-dimer positive: Go to protocol for moderate- or high-risk patient.

Moderate-risk patient: or High-risk patient:

Order D-dimer test and either ventilation-perfusion (V/Q) scan or helical computed tomographic (CT) scan (the latter is preferred if the patient has chronic pulmonary disease):

- ☐ Normal V/Q scan: PE ruled out. †
☐ High-probability V/Q scan or positive helical CT scan: PE diagnosed. ‡
☐ Nearly normal V/Q scan, low- or intermediate-probability V/Q scan, or any other helical CT result. Order bilateral ultrasonography of leg veins:
☐ Positive ultrasound examination: PE diagnosed. §
☐ Negative ultrasonography: Base further evaluation on initial clinical risk assessment examination:
☐ Low-risk patient: PE ruled out. ¶
☐ Moderate-risk patient and negative D-dimer test: PE ruled out. ¶
☐ High-risk patient and positive D-dimer test: PE ruled in (consider angiography to confirm diagnosis). ¶
☐ Moderate-risk patient and positive D-dimer test, or high-risk patient and negative D-dimer test. Choose one of the following options and manage according to the results:

- ☐ Serial ultrasonography at 1 and 2 weeks:
☐ Positive ☐ Negative
☐ Helical CT scan (if not already ordered):
☐ Positive ☐ Negative§
☐ V/Q scan (if not already ordered):
☐ Positive ☐ Negative§
☐ Pulmonary angiography:
☐ Positive ☐ Negative

Assessment/plan

*—Less than 2 percent PE with moderately sensitive D-dimer test (85 to 98 percent) and less than 1 percent PE with highly sensitive D-dimer test (greater than 98 percent).

†—Approximately 1 percent with PE.

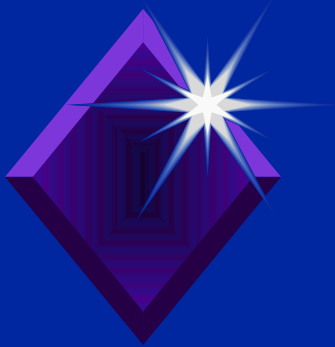
‡—Positive helical CT indicates intraluminal filling defects in segmental or larger pulmonary arteries.

§—Consider serial bilateral ultrasonography examination of proximal leg veins in patients with negative results.

¶—Preferred in the following instances: if a subsegmental intraluminal filling defect is seen on initial helical CT scan; if there is a high-probability V/Q scan in a low-risk patient; if serial testing is not feasible; or if symptoms are severe and there is a need to exclude PE from the differential diagnosis.

Developed by Mark H. Ebell, M.D., M.S., Michigan State University College of Human Medicine, East Lansing. Copyright © 2004 American Academy of Family Physicians. Physicians may photocopy or adapt for use in their own practice; all other rights reserved. "Point-of-Care Guides," Ebell MH. American Family Physician. February 1, 2004;69:599-601. www.aafp.org/afp/20040201/pocform.html

Ebell MH, AFP 2004;69(3):599; FPM Feb 2004; :61



Pre-test
Probability



D-
dimer



Diagnostic
Study

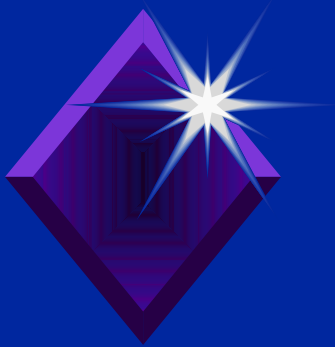
VQ or CT



Further
Studies

Treat

Follow



Low Pre-test
Probability



D-dimer

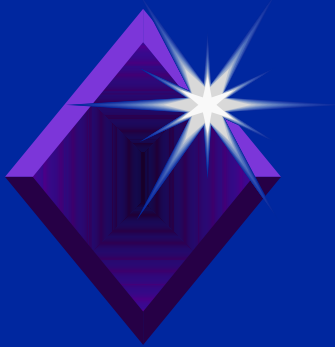
Neg

Pos

Ruled
Out

CT or
VQ





High or Intermediate Pre-test Probability

CT or VQ

neg

Ruled Out

pos

Treat

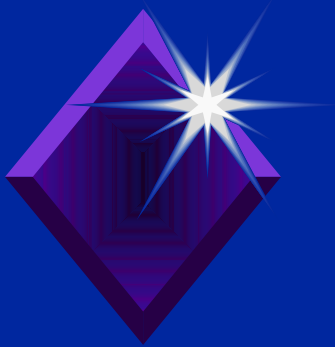
Indeterminant Ct or Intermed VQ

pos

LE US

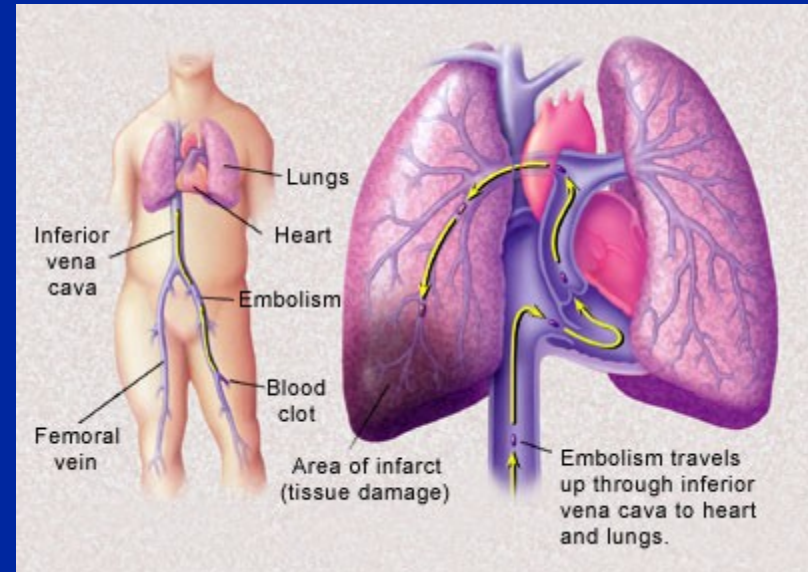
neg

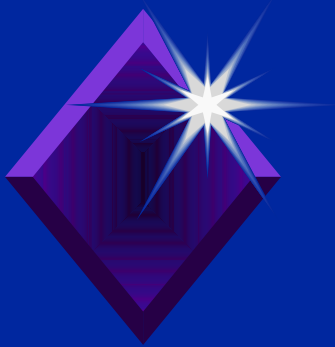
Mod risk & neg D-dimer-ruled out
High risk & pos D-dimer-ruled in
Mod risk and pos D-dimer



Treatment Options

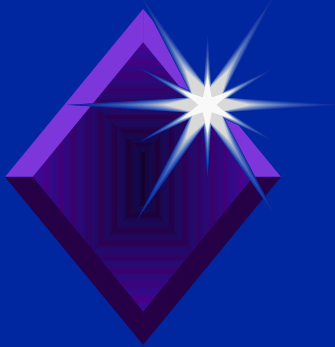
- ◆ **Anticoagulation**
- ◆ **Thrombolytics**





Anticoagulation

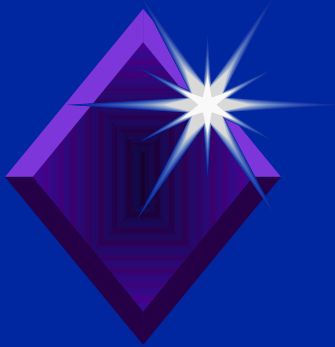
- ◆ **Prevent further embolization**
- ◆ **IV Heparin for 5 days**
 - ◆ **Or LMWH**
- ◆ **Coumadin starting as early as day 1 Heparin with 4 day overlap**
 - ◆ **duration same as for DVT**



Thrombolysis

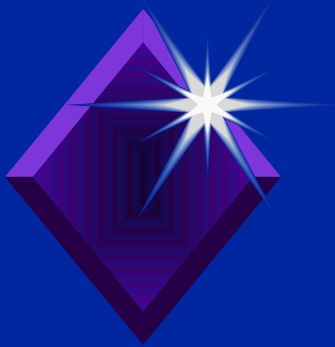
Benefits

- ◆ Accelerated clot lysis and tissue perfusion
- ◆ Decreased mortality
- ◆ Reversal of right heart failure
- ◆ Decreased recurrence
- ◆ Decrease Pulmonary HTN



Prognosis

- ◆ **If untreated survival is 70%
(death 2^o recurrent PE)**
- ◆ **Treated survival = 92%**
- ◆ **Majority of deaths occur before
therapy initiated or condition
recognized**

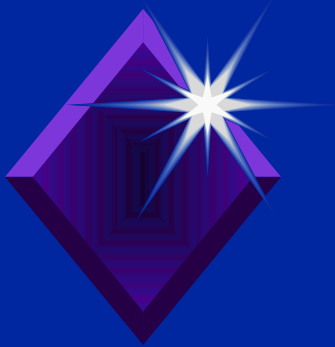


Prevention

- ◆ Same as for DVT
- ◆ Identify high risk patients and institute recommended protocols

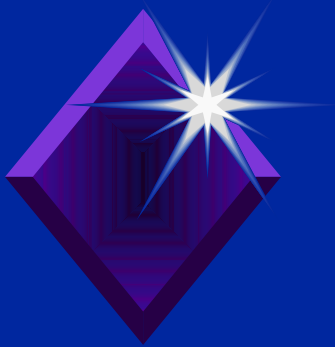
WWW.DVT.NET





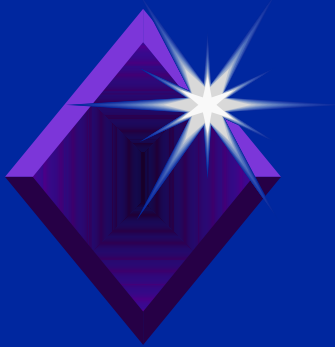
What to do with the idiopathic DVT?

***(Risk of cancer or
hypercoagulable state)***



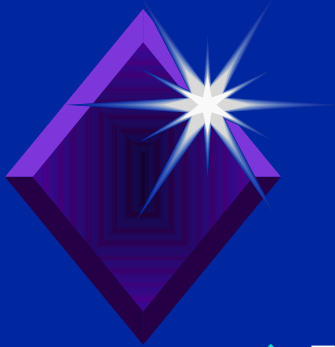
Hypercoagulable W/U

- ◆ Age < 40
- ◆ Thrombus in unusual locations
- ◆ Upper extremity, neck, anterior abd wall, eye, CNS
- ◆ Recurrent thrombotic events without incident causation
- ◆ Recurrent thrombotic events when on anticoagulants in therapeutic range
- ◆ Thrombotic events in absence of underlying illness or medication
- ◆ Family history of thrombotic events or hypercoagulability
- ◆ Bilateral symmetric thrombotic events (bilateral DVT)



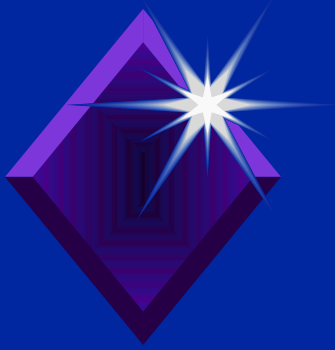
Hypercoagulable Labs

- ◆ **CBC, PT/PTT**
- ◆ **ANA**
- ◆ **Protein C & S**
- ◆ **APC resistance (Factor V Leiden mutation)**
- ◆ **Antiphospholipid antibody**
- ◆ **Antithrombin III**
- ◆ **Fibrinogen & plasminogen**
- ◆ **Prothrombin 20210A Mutation**

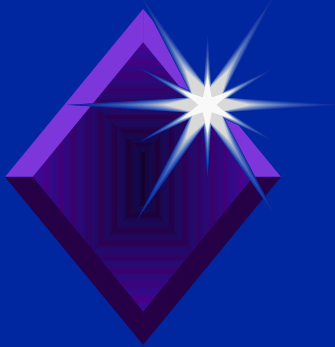


Risk of cancer?

- ◆ **Increased risk of discovering cancer in the < 60 age group**
- ◆ **2/3 adenocarcinoma**
 - ◆ **GI - 25%**
 - ◆ **Urogenital - F12%; M 16%)**
 - ◆ **Hematologic - 10%**
- ◆ **Highest risk in first 6 months**
- ◆ **H&P, CBC,ESR, Chem 20, PSA, Guiac**
- ◆ **NEJM 1998;338:1169**
 - ◆ **15,348 DVT & 11,305 PE**
 - ◆ **1737 cancer (est. 1372)**

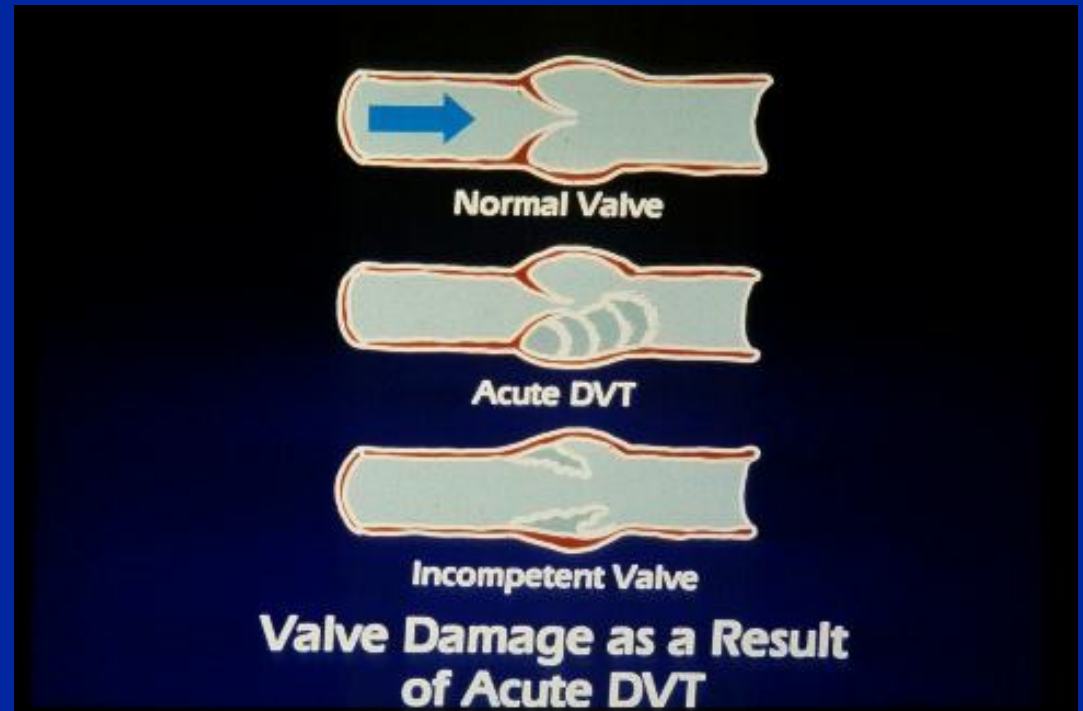


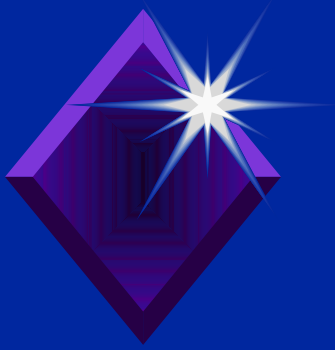
***Post Thrombotic
Syndrome
(Post Phlebitic
Syndrome)***



Definition

- ◆ Incompetent lower extremity venous valves result in ambulatory venous hypertension

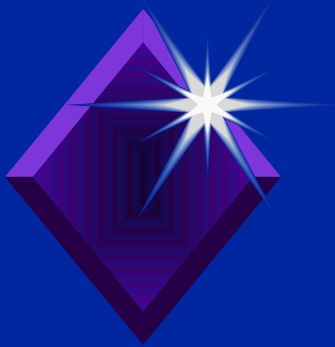




Findings

- ◆ **Edema**
- ◆ **Soft tissue fibrosis**
- ◆ **Ulceration**
- ◆ **Pain**

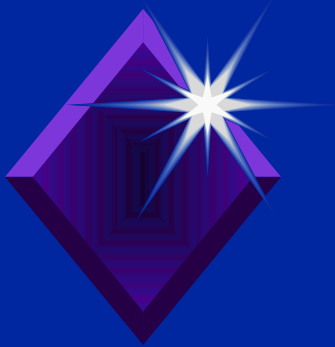




Management

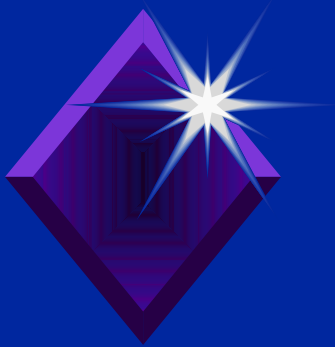
- ◆ **Compression stockings**
- ◆ **Surgical (goal is ulcer healing and decreased pain)**
 - ◆ **Perforator Interruption**
 - ◆ new laparoscopic technique
 - ◆ **Valve Repair**
 - ◆ symptom relief 65%
 - ◆ ulcer healing approx. 65% (@5 yrs)





Management

- ◆ **Major treatment is prevention of DVT**
- ◆ **More aggressive treatment of DVT - Thrombolytics**



Conclusion

- ◆ **Thromboembolism is a common primary care problem**
- ◆ **Clinical suspicion is still quite important**
- ◆ **Careful use of diagnostic exams**
- ◆ **Use LMWH**
- ◆ **Survey for Hypercoagulability**